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(71) Applicant *(for all designated States except US)*: SCHERING AGROCHEMICALS LIMITED [GB/GB]; Hauxton, Cambridge CB2 5HU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MELLOR, Michael [GB/GB]; RIORDAN, Peter, Dominic [GB/GB]; Chesterford Park Research Station, Saffron Walden, Essex CB10 1XL (GB).

(74) Agent: WALDMAN, Ralph, David; Schering Agrochemicals Limited, Industrial Property Department, Chesterford Park Research Station, Saffron Walden, Essex CB10 1XL (GB).

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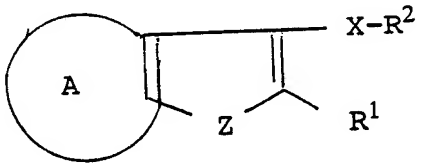

(I)

(57) Abstract

Compounds of formula (I) where ring A is an optionally substituted six membered ring containing one or two nitrogen atoms; X is O, S or -NR^3-; R^1 is Q, cyano, halogen or nitro; Q is hydrogen, acyl, -$C(=W)R^5$, -SR^3, -$C(=NR^3)NR^4R^5$, -$C(=NR^3)OR^4$, -$C(OR^5)R^3R^4$, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl; R^2 is Q, or -$SiR^3R^4R^5$, or when X is O or NR^3, can also be -NR^4R^5, or when X is NR^3, can also be -OR^4; W is NR^3, NOR^3 or NNR^4R^5; Z is $S(O)_n$ or O; R^3, R^4 and R^5, which may be the same or different, are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl or R^3 and R^4 or R^4 and R^5 together with the atom to which they are attached can form a ring; and n is 0, 1 or 2 can be used for combating phytopathogenic fungi. Many of the compounds are novel.

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Title: Biheterocyclic fungicidal compounds

Field of the invention

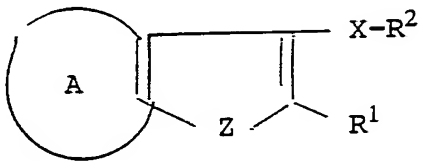
This invention relates to new phytopathogenic fungicides based on thiophene or furan rings to which is fused a nitrogen containing ring.

Prior Art

In EP 403 885, there are disclosed, inter alia, 3-hydroxy-thienopyridines as endoparasiticides. We have found that some of these compounds have activity against phytopathogenic fungi. We have also found that many related compounds, many of which are novel, also have fungicidal activity. There are many other references to thieno- and furano- pyridines and pyrimidines and related structures but very few disclose compounds where there is an optionally substituted hydroxy, mercapto or amino group in the 3-position and none of this type where the compounds have been described as having phytopathogenic fungicididal activity. Exceptions are BE 848 654 and EP 452 002, which disclose certain specific thieno[2,3-d]pyrimidines. In other disclosures of fungicidal thieno[2,3-d]pyrimidines, the 3 substituent is for example alkyl, eg Japanese Kokai 56053681, 56059778, 56034683 and 56008389. Canadian patent 1232904 discloses thieno[2,3-d]pyrimidines to which is fused a third ring but the compounds are disclosed as antimycotic agents against human pathogenic fungi. No mention is made of activity against phytopathogenic fungi. USP 4,767,766 discloses derivatives of certain 3-hydroxy-thienopyridines as 5-lipooxygenase inhibitors.

Disclosure of the invention

According to the invention there is provided the use for combating phytopathogenic fungi, of a compound of formula I



(I)

where

ring A is an optionally substituted six membered ring containing one or two nitrogen atoms;

X is O, S or $-NR^3-$;

R^1 is Q, cyano, halogen or nitro;

Q is hydrogen, acyl, $-C(=W)R^5$, $-SR^3$, $-C(=NR^3)NR^4R^5$, $-C(=NR^3)OR^4$, $-C(OR^5)R^3R^4$, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl;

R^2 is Q, or $-SiR^3R^4R^5$, or when X is O or NR^3, can also be $-NR^4R^5$, or when X is NR^3, can also be $-OR^4$;

W is NR^3, NOR^3 or NNR^4R^5;

Z is $S(O)_n$ or O;

R^3, R^4 and R^5, which may be the same or different, are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl or R^3 and R^4 or R^4 and R^5 together with the atom to which they are attached can form a ring;

and

n is 0, 1 or 2, together with salts of compounds which are acidic and also complexes with metal salts.

with the proviso that when the compound is a thieno[2,3-d]pyrimidine, where X is O and R^2 is (halo)alkyl, it is not substituted in the 4-position by optionally substituted amino.

Many of the compounds of formula I are novel and the invention thus includes all such novel compounds and especially those compounds where the groups are as defined above with the provisos, when Z is S:

(i) X is not NR^3, where R^3 is hydrogen;

(ii) when X is oxygen and R^2 is hydrogen, optionally substituted alkyl, cycloalkyl, $-COR^3$, $-COOR^3$, $-CONR^3R^4$ or $-COSR^3$, then R^1 is not optionally substituted alkyl (except cyanoalkyl), optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heteroaryl,

(iii) when ring A is pyrido, with the N-atom in the 5-position, the ring is not monosubstituted in the 4-position by aroyl or in the 4 or 6 position by methyl,

(iv) when ring A is pyrido, with the N-atom in the 6-position, R^1 is not hydrogen or methyl,

(v) when ring A is pyrido, with the N-atom in the 7-position, X is oxygen and R^2 is hydrogen, then R^1 is not a) COD or C(=NH)D, where D is optionally substituted alkoxy, optionally substituted cycloalkoxy or $-NR^3R^4$, nor b) $-C(=NR^3)NR^4R^5$, in which R^3 and R^4 together with the atom to which they are attached form a 5 or 6 membered ring, and

(vi) when ring A is pyrido, with the N-atom in the 7-position, the ring is not monosubstituted in the 4-position by amino or methyl.

(vii) when the compound is a thieno[2,3-d]pyrimidine, carrying a ring fused to the pyrimidine it is not substituted in the 4-position by oxo.

(viii) when the compound is a thieno[2,3-d]pyrimidine, and X is S, R^2 is not hydrogen.

(ix) when ring A is pyrido, with the N-atom in the 5-position, it is not a tetrahydropyrido ring,

and with the further proviso that when Z is O or S and ring A is pyrido, the pyrido ring does not carry an imidazolinyl grouping.

Certain individual compounds which might be excluded by the generalities of the provisos are novel and the invention includes these. Example of such compounds are the isopropyl, cyclohexyl and benzyl esters of 3-hydroxythieno[2,3-b]pyridine-2-carboxylic acid, as well as 3-hydroxythieno[2,3-b]pyridine, substituted in the 2 position by phenylcarbamoyl, furyl, pyrid-2-yl, 5-phenyl-oxazol-2-yl or benzoxazol-2-yl.

Some novel compounds of formula I have weak pesticidal activity but still have utility as intermediates and such compounds also form one aspect of the invention.

Optional substituents on ring A include hydrogen, hydroxy, halogen, cyano, $-COOR^3$, $-COR^3$, $-NR^3R^4$, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylthio or heterocyclyl. Preferred substituents are hydroxy, halogen, cyano, $-COR^3$, $-NR^3R^4$, alkyl, alkoxy, aryloxy, $S(O)_nR^3$ or heterocyclyl. Especially preferred substituents are hydroxy, chloro, cyano, amino, diethylamino, methyl, methoxy, phenoxy, methylthio, isopropylthio, methylsufinyl, methylsulfonyl or 2-thienyl.

Alternatively or additionally two adjacent substituents on ring A together with the attached atoms of ring A, may together form an additional fused ring. This additional ring is preferably 5 or 6-membered and may contain heteroatoms e.g. nitrogen and/or oxygen and/or sulfur. The additional ring may itself be substituted by hydrogen, hydroxy, halogen, cyano, $-CO_2R^3$, $-COR^3$, $-NR^3R^4$, optionally

substituted alkyl, optionally substituted alkoxy, optionally substituted aryloxy, optionally substituted alkylthio groups or may be fused to a further benzene ring.

The ring A is preferably aromatic but with subsequent fusion, the ring A and the additional ring(s) may be aromatic and/or non-aromatic. Examples of such additional rings are benzo-, pyrido, thiazolo and benzothiazolo.

Alkyl groups are preferably of 1 to 20, eg 1 to 6, carbon atoms. Alkenyl and alkynyl groups are generally of 3 to 6 carbon atoms. Cycloalkyl groups are preferably of 3 to 8 carbon atoms.

Substituents, when present on any alkyl, cycloalkyl, alkenyl or alkynyl group, include halogen, cyano, alkoxy (e.g. of 1 to 4 carbon atoms, and which may be optionally substituted, e.g. by halo), hydroxy, alkylthio, nitro, optionally substituted amino, carboxy, alkoxycarbonyl, acyl, acyloxy, aryl, heterocyclyl and trialkylsilyl.

Preferred substituents on any alkyl group are cyano, optionally substituted alkoxy, alkylthio, optionally substituted amino, alkoxycarbonyl, acyl, aryl and heterocyclyl and examples of such substituents include 2-trimethylsilylethoxy, methoxyethoxy, ethylthio, methoxycarbonyl, isopropoxycarbonyl, acetyl, phenyl, thiazolyl, morpholino, phthalamido, 2-oxopyrrolidino, 2-oxobenzoxazolin-3-yl.

Preferred substitutents on any alkenyl group are cycloalkyl, halogen, cyano, aryl, alkoxycarbonyl, acyl and heterocyclyl, and examples of such substituents include phenyl, methoxycarbonyl and cyclohexyl.

Preferred substituents on any alkynyl group are halogen, optionally substituted alkyl, trialkylsilyl, phenyl, acyl and alkoxycarbonyl and examples of such substituents include iodo, methyl, hydroxymethyl, trimethylsilyl and phenyl.

Cycloalkyl groups may also be substituted by alkyl.

Aryl groups are usually phenyl, optionally substituted, e.g. by halogen, optionally substituted alkyl or alkoxy, aryl, aryloxy, nitro, optionally substituted amino, $-COOR^3$, CN, $CONR^3R^4$ or $S(O)_nR^3$, where n is 0 to 2. Preferred substituents on the aryl group are chloro, methyl, trifluoromethyl, methoxy, nitro, amino or cyano.

The term heterocyclyl includes both aromatic and non-aromatic heterocyclyl groups. Heterocyclyl groups are generally 5 or 6-membered rings containing up to 3 heteroatoms from nitrogen, oxygen and sulfur. The heterocyclyl groups may be fused to a benzene ring to form a fused heterocyclyl group. Examples of heterocyclyl groups are thienyl, furyl, pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, thiazolinyl, oxazolyl, benzimidazolyl, tetrazolyl, benzoxazolyl, thiadiazolyl, dioxolanyl, imidazopyridinyl, 1,3-benzoxazinyl, 1,3-benzothiazinyl, oxazolopyridinyl, triazolyl, triazinyl, imidazolyl, morpholino, benzofuranyl, pyrazolinyl, quinolinyl, quinazolinyl, sulfolanyl, dihydroquinazolinyl, benzothiazolyl, piperidinyl, phthalamido, 2-oxopyrrolidino, 2-oxobenzoxazolin-3-yl. and benzofuranyl. Preferred heterocyclyl groups are thienyl, furyl, pyridyl, sulfolanyl, pyrimidinyl, thiazolyl, morpholino, phthalimido, piperidinyl, 2-oxopyrrolidino, 2-oxobenzoxazolin-3-yl, triazolyl, benzoxazolyl, oxazolyl and benzofuranyl. The

heterocyclyl groups may themselves be substituted for example as for phenyl, with the preferred substituents being methyl, methoxycarbonyl and ethoxycarbonyl.

Amino groups may be substituted for example by one or two optionally substituted alkyl, acyl or sulfonyl groups, e.g. by isopropyl, butyl, 5-cyanopentyl, cyclohexyl, acetyl, trifluoroacetyl, trifluoromethylsulfonyl, or two substituents can form a ring for example a piperidino or morpholino ring.

The term acyl includes the residue of sulfur and phosphorus-containing acids as well as carboxylic acids. Examples of acyl groups are thus $-COR^3$, $-COOR^3$, $-CYNR^3R^4$, $-CON(R^3)OR^4$, $-COONR^3R^4$, $-CON(R^3)NR^4R^5$, $-COSR^3$, $-CSSR^3$, $-S(O)_pR^3$, $-S(O)_2OR^3$, $-S(O)_pNR^3R^4$, $-P(=Y)(OR^3)(OR^4)$, $-CO-COOR^3$, where p is 1 or 2 and Y is O or S.

When R^3 and R^4 or R^4 and R^5 together with the atom to which they are attached form a ring, this is generally a 5 to 7-membered ring which may be substituted and may contain other heteroatoms, for example morpholine, thiomorpholine, piperidine, imidazole or triazole.

It will be evident to those skilled in the art that in certain compounds of formula I, for example where R^2 is hydrogen or where the ring A is fused with a benzene ring to form a thieno[2,3-b]quinoline ring system, which is substitued at the 4 position by a hydroxy group, there exists the possibility of tautomeric forms of these molecules. These tautomers and any mixtures thereof form part of the invention. It will also be appreciated that some compounds may comprise a group with a chiral carbon atom resulting in the possibility of enantiomers and the invention includes individual enantiomers as well as

mixtures of these. The invention also includes individual geometric isomers where these may exist.

In preferred compounds Z is preferably S. Ring A is preferably unsubstituted. Ring A is preferably pyrido whose nitrogen is in the 7-position.

Particularly preferred values for R^2 are hydrogen, acyl, optionally substituted alkynyl and optionally substituted alkyl and especially propargyl, cyanoalkyl, benzyl and cyanoalkylcarbamoyl, alkanoyl and alkoxycarbonyl.

Particularly preferred values for R^1 are heterocyclyl, especially furyl, and acyl, especially COR^3 or $COOR^3$, where R^3 is optionally substituted alkyl, optionally substituted amino, aryl or cycloalkyl.

Salts of compounds of the invention are usually those of agriculturally acceptable metal cations or of organic bases, especially tertiary amines.

Complexes of compounds of the invention are usually formed from a salt of formula MAn_2, in which M is a divalent metal cation, e.g. copper, manganese, cobalt, nickel, iron or zinc and An is an anion, e.g. chloride, nitrate or sulfate.

The compounds of the invention have activity against a wide range of pathogens of Deuteromycete, Ascomycete, Phycomycete and Basidiomycete origin, and especially against fungal diseases of plants, e.g. mildews and particularly barley powdery mildew (Erysiphe graminis) and vine downy mildew (Plasmopara viticola), rice blast (Pyricularia oryzae), cereal eyespot (Pseudocercosporella herpotrichoides), rice sheath blight (Pellicularia

sasakii), grey mould (Botrytis cinerea), apple scab (Venturia inaequalis) and glume blotch (Leptosphaeria nodorum).

The compounds of the invention are generally formulated in conventional compositions used for fungicides. These compositions can contain one or more additional pesticides, for example compounds known to possess herbicidal, fungicidal, insecticidal, acaricidal or nematicidal properties.

The diluent or carrier in the composition of the invention can be a solid or a liquid optionally in association with a surface-active agent, for example a dispersing agent, emulsifying agent or wetting agent. Suitable surface-active agents include anionic compounds such as a carboxylate, for example a metal carboxylate of a long chain fatty acid; an N-acylsarcosinate; mono- or di-esters of phosphoric acid with fatty alcohol ethoxylates or salts of such esters; fatty alcohol sulfates such as sodium dodecyl sulfate, sodium octadecyl sulfate or sodium cetyl sulfate; ethoxylated fatty alcohol sulfates; ethoxylated alkylphenol sulfates; lignin sulfonates; petroleum sulfonates; alkyl-aryl sulfonates such as alkyl-benzene sulfonates or lower alkylnaphthalene sulfonates, e.g. butyl-naphthalene sulfonate; salts of sulfonated naphthalene-formaldehyde condensates; salts of sulfonated phenol-formaldehyde condensates; or more complex sulfonates such as the amide sulfonates, e.g. the sulfonated condensation product of oleic acid and N-methyl taurine or the dialkyl sulfosuccinates, e.g. the sodium sulfonate of dioctyl succinate. Nonionic agents include condensation products of fatty acid esters, fatty alcohols, fatty acid amides or fatty-alkyl- or alkenyl-substituted phenols with ethylene oxide, fatty esters of polyhydric alcohol ethers, e.g. sorbitan fatty

acid esters, condensation products of such esters with ethylene oxide, e.g. polyoxyethylene sorbitan fatty acid esters, block copolymers of ethylene oxide and propylene oxide, acetylenic glycols such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol, or ethoxylated acetylenic glycols. Examples of a cationic surface-active agent include, for instance, an aliphatic mono-, di-, or polyamine as an acetate, naphthenate or oleate; an oxygen-containing amine such as an amine oxide or polyoxyethylene alkylamine; an amide-linked amine prepared by the condensation of a carboxylic acid with a di- or polyamine; or a quaternary ammonium salt.

The compositions of the invention can take any form known in the art for the formulation of agrochemicals, for example, a solution, a dispersion, an aqueous emulsion, a dusting powder, a seed dressing, a fumigant, a smoke, a dispersible powder, an emulsifiable concentrate or granules. Moreover it can be in a suitable form for direct application or as a concentrate or primary composition which requires dilution with a suitable quantity of water or other diluent before application.

As a dispersion, the composition comprises a compound of the invention dispersed in a liquid medium, preferably water. It is often convenient to supply the consumer with a primary composition which can be diluted with water to form a dispersion having the desired concentration. The primary composition can be provided in any one of the following forms. It can be a dispersible solution which comprises a compound of the invention dissolved in a water-miscible solvent with the addition of a dispersing agent. A further alternative comprises a compound of the invention in the form of a finely ground powder in association with a dispersing agent and intimately mixed

with water to give a paste or cream which can if desired be added to an emulsion of oil in water to give a dispersion of active ingredient in an aqueous oil emulsion.

An emulsifiable concentrate comprises a compound of the invention dissolved in a water-immiscible solvent together with an emulsifying agent and which is formed into an emulsion on mixing with water.

A dusting powder comprises a compound of the invention intimately mixed with a solid pulverulent diluent, for example, kaolin.

A granular solid comprises a compound of the invention associated with similar diluents to those which may be employed in dusting powders, but the mixture is granulated by known methods. Alternatively it comprises the active ingredient adsorbed or absorbed on a pre-granular diluent, for example, Fuller's earth, attapulgite or limestone grit.

A wettable powder usually comprises the active ingredient in admixture with a suitable surfactant and an inert powder diluent such as china clay.

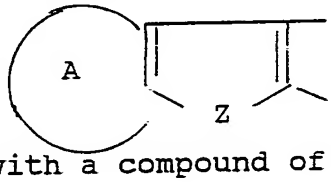
Another suitable concentrate, particularly when the product is a solid, is a flowable suspension concentrate which is formed by grinding the compound with water, a wetting agent and a suspending agent.

The concentration of the active ingredient in the composition of the present invention is preferably within the range of 1 to 30 per cent by weight, especially 5 to 30 per cent by weight. In a primary composition the

amount of active ingredient can vary widely and can be, for example, from 5 to 95 per cent by weight of the composition.

The novel compounds of the invention may be prepared in known manner, in a variety of ways, for example

a) by reacting a compound of formula II,



(II)

(i) with a compound of formula R^2L, where L is a leaving group, such as halogen, in the presence of a base, or

(ii) with a compound of formula R^2OH, for example in the presence of triphenylphosphine and diethyl azodicarboxylate, or

(iii) with a compound of formula R^3NCO, for example in the presence of a base, to give a compound where R^2 is $CONHR^3$, or

b) by reacting a compound of formula I, where X is O

(i) with a compound of formula R^2SH, to give a compound where X is S, or

(ii) with a compound of formula R^3R^4NH, to give a compound where XR^2 is $-NR^3R^4$, or

c) by reacting a compound of formula I, where R^1 is $-COOR^3$ and R^3 is not hydrogen,

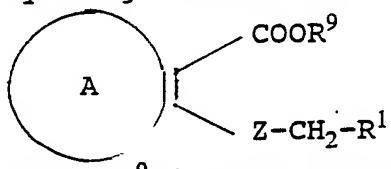
(i) with a base to give a compound where R^3 is hydrogen, or

(ii) with a compound of formula R^3R^4NH, to give a compound where R^1 is $-CONR^3R^4$, or

d) by reacting a compound of formula I, where X is NH and R^2 is hydrogen, with a suitable anhydride to give a compound where R^2 is $-COR^3$ or $-SO_2R^3$.

The compounds of formula II are known or can be prepared in known manner, for example

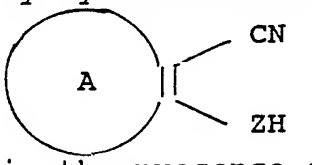
a) by ring closure of a compound of formula III



(III)

where R^9 is for example hydrogen or alkyl. Compounds of formula III where Z is S(O)p, where p is 1 or 2, may be prepared by oxidation of the corresponding compound III in which Z = S, using coventional oxidising agents, for example metachloroperbenzoic acid, hydrogen peroxide or sodium metaperiodate, in a suitable solvent; or

b) by cyclisation of a compound of formula IV

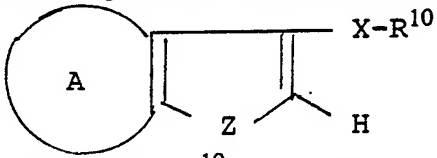


(IV)

in the presence of a compound, R^1CH_2L and a base, to give a compound where X is NH and R^2 is H.

Examples of bases used for the above reactions include alkali metal compounds, such as hydrides,. e.g. sodium hydride, alkoxides, e.g. sodium methoxide, carbonates e.g. potassium carbonate, and organic bases, such as 1,4-diaza-bicyclo[2.2.2.]octane.

An alternative method for preparing novel compounds of the invention comprises reacting a compound of formula V



(V)

where X is O and R^{10} is alkyl or acyl, with a lithium base at reduced temperature in a suitable solvent and subsequently reacting the resulting lithio species with a suitable electrophile.

Examples of lithium bases include n-butyllithium, sec-butyllithium, tert-butyllithium and lithium diisopropylamide.

Examples of suitable electrophiles are alkyl halides, nitrites, ketones, aldehydes, esters, tosylates, mesylates and sulfones.

Suitable solvents include optionally chlorinated hydrocarbons, 1,2-dichlorobenzene; ethers, such as tetrahydrofuran; ketones, such as 2-butanone; nitriles, such as acetonitrile; amides, such as dimethylformamide, and alcohols such as methanol and isopropanol

Compounds of formula I can be modified in other known ways to give other compounds of the invention. For example, a compound where XR^2 is $-OP(=O)(OR^3)(OR^4)$, can be reacted with a compound R^2-SH, to give a compound where X is S and R^2 is a new group. In the case where this new group is a benzyl group, the compound can be reacted with N-chloro-succinimide followed by R^2L, in the presence of a base, to give other values of R^2.

Other methods will be apparent to the chemist skilled in the art as will be the methods for preparing starting materials and intermediates. For example, compounds of formula III or IV may be prepared by general methodology as outlined in Comprehensive Heterocyclic Chemistry, ed. A.R. Katritzky and C.W. Rees, Pergamon, 1984. The Examples also make apparent various methods of preparing compounds of the invention as well as starting materials and intermediates.

The invention is illustrated in the following Examples. Structures of isolated novel compounds were confirmed by elemental and/or other appropriate analyses. Temperatures are in °C.

Example 1

Sodium hydride (1.22 g) was added to a stirred solution of isopropyl 2-chloronicotinate (10 g) and isopropyl mercaptoacetate (6.72 g) in dimethylformamide (100 ml) at room temperature. After stirring for 2 hours, the mixture was poured into ice-water (600 ml). The solid was filtered and dried to give the intermediate isopropyl 2-(isopropoxycarbonylmethylthio)nicotinate, (m.p. 60.5-1.5°). A solution of this intermediate (2.95 g) in isopropanol (50 ml) was treated with sodium hydride (0.24 g). The mixture was stirred at room temperature for 19 hours, poured into water (500 ml), and acidified with acetic acid to produce a white solid, which was collected by filtration, washed with water, dried and recrystallised from isopropanol to give isopropyl 3-hydroxythieno-[2,3-b]pyridine-2-carboxylate, m.p. 79-81°, (Compound 1).

Example 2

A stirred mixture of Compound 1 (3.0 g) and anhydrous potassium carbonate (1.75 g) in 2-butanone (50 ml) was heated at reflux for 1 hour. Bromoacetonitrile (1.52 g) was then added and the mixture stirred at reflux for a further 1 hour. The reaction mixture was then poured into water and extracted with ether. The extracts were dried and evaporated to give an oil which solidified on standing. Recrystallisation from ethyl acetate/hexane gave isopropyl 3-(cyanomethoxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 88°, (Compound 2).

Example 3

A mixture of Compound 1 (2.0 g), diethyl azodicarboxylate (1.46 g), triphenylphosphine (2.20 g) and methanol (0.27 g) in tetrahydrofuran (50 ml) was stirred at room temperature for 24 hours. The solvent was evaporated and the residue subjected to column chromatography to give isopropyl 3-methoxythieno[2,3-b]pyridine-2-carboxylate, as a pale brown oil, (Compound 3).

Example 4

A mixture of Compound 3 (1.0 g) and 1M methanolic sodium methoxide solution (40 ml) was heated on a steam bath for 15 minutes. After cooling, the mixture was acidified with 3M hydrochloric acid and the solid collected and dried to give 3-methoxythieno[2,3-b]pyridine-2-carboxylic acid, m.p. 223° (dec), (Compound 4).

Example 5

A solution of compound 3 (1.0 g) in n-butylamine (15 ml) was refluxed for 14 hours. Following evaporation of the unreacted n-butylamine, the residue was partitioned between ether and water. The organic phase was dried and evaporated to give a crude product as a yellow oil. Column chromatography gave isopropyl 3-(butylamino)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 53-4.5°, (Compound 5a) and N-butyl-3-methoxythieno[2,3-b]pyridine-2-carboxamide, m.p. 101-4°, (Compound 5b).

Example 6

[2-(Chloromethoxy)ethyl]trimethylsilane (3.0 g) was added to a stirred solution of Compound 1 (1.42) and N,N-diisopropylethylamine (3.48 g) in dichloromethane (3 ml). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 hours and was then purified by silica gel column chromatography to

give isopropyl 3-[2-(trimethylsilyl)ethoxymethoxy]thieno-[2,3-b]pyridine-2-carboxylate, as a light brown oil, (Compound 6).

Example 7

4-Chlorobenzoyl chloride (1.93 g) was added to a stirred mixture of Compound 1 (2.37 g) and triethylamine (1.11 g) in dioxane (150 ml). After stirring for 18 hours, the reaction mixture was filtered and the filtrate evaporated. The residue was dissolved in ether and the solution washed with saturated aqueous sodium bicarbonate and water before drying and evaporating to give the crude product. Recrystallisation from hexane gave isopropyl 3-(4-chlorobenzoyloxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 137-8°, (Compound 7).

Example 8

A suspension of Compound 1 (2.1 g) in 1M aqueous sodium hydroxide (200 ml) was heated on a steam bath for 3 hours. The mixture was then acidified with 3M hydrochloric acid and extracted with ether. Evaporation of the dried extracts gave the intermediate 3(2H)-thieno-[2,3-b]pyridinone, as a pink solid (m.p. 84°). The intermediate (0.2 g) was heated at reflux in 2-butanone with anhydrous potassium carbonate (0.18 g) for 15 minutes. Bromoacetonitrile (0.16 g) was then added and the mixture refluxed for a further 5 hours. The solvent was evaporated and the residue partitioned between water and ethyl acetate. Evaporation of the dried organic phase gave a brown gum which was purified by silica gel column chromatography to give 3-(cyanomethoxy)thieno-[2,3-b]pyridine, m.p. 85-8°, (Compound 8).

Example 9

A solution of Compound 1 (2.37 g) in aniline (25 ml) was stirred at reflux for 7 hours. On cooling, the solid which crystallised out, was collected by filtration and washed with ether and then 2N hydrochloric acid and water, before drying to give 3-hydroxy-N-phenylthieno[2,3-b]pyridine-2-carboxamide, m.p. 247-8°, (Compound 9).

Example 10

A solution of Compound 1 (2.37 g) in tetrahydrofuran (10 ml) was added over 15 minutes, to a stirred suspension of sodium hydride (0.40 g) in tetrahydrofuran (5 ml) cooled to 5-10°. After stirring for a further 15 minutes diethyl phosphorochloridate (1.69 g) in tetrahydrofuran (5 ml) was added dropwise. After stirring at room temperature for 3.5 hours the reaction mixture was poured into ice water (50 ml), acidified with 2N hydrochloric acid and extracted with ethyl acetate. The extracts were dried and evaporated to give the crude product, which was purified by silica gel column chromatography, to give isopropyl 3-(diethoxyphosphinyloxy)thieno[2,3-b]pyridine-2-carboxylate as an oil, (Compound 10).

Example 11

A stirred mixture of Compound 1 (3.0 g), 6-isocyanato-hexanenitrile (1.80 g) and acetonitrile (7 ml), containing a catalytic quantity of 1,4-diazabicyclo[2,2,2]octane, was heated at reflux for 14 hours. Following evaporation of the solvent, the crude product was purified by silica gel column chromatography and then recrystallised from di-isopropyl ether to give isopropyl 3-(5-cyanopentyl-carbamoyloxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 72.5-4°, (Compound 11).

Example 12

Methanesulfonyl chloride (1.69 g) was added to a stirred mixture of Compound 1 (2.0 g) and anhydrous potassium carbonate (8.0 g) in acetone (40 ml) and the resultant mixture stirred at room temperature for 19 hours. The mixture was filtered and the filtrate evaporated to give a residue which was recrystallised from 2-butanone to give isopropyl 3-(methylsulfonyloxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 125-7°, (Compound 12).

Example 13

Sodium hydride (1.8 g) was added to a stirred solution of 2-chloronicotinonitrile (10.0 g) and isopropyl mercaptoacetate (9.67 g) in dimethylformamide (150 ml). After stirring at room temperature for 5.5 hours, the reaction mixture was poured into water (1000 ml) to give an orange solid. The solid was collected by filtration, washed with water and dried. Recrystallisation of the solid, first from acetonitrile and then isopropanol gave isopropyl 3-aminothieno[2,3-b]pyridine-2-carboxylate, m.p. 179.5-80.5°, (Compound 13).

In a similar manner, there was also obtained cyclohexyl 3-amino-5-chloro-4,6-dimethylthieno[2,3-b]pyridine-2-carboxylate, m.p. 179-81°. (Compound 13a)

Example 14

A stirred mixture of methyl 3-bromoisonicotinate (5.70 g), isopropyl mercaptoacetate (3.54 g), anhydrous potassium carbonate (5.46 g) and acetonitrile (80 ml) was heated at reflux for 24 hours. The mixture was then poured into water (400 ml) and extracted with ethyl acetate. The aqueous phase was acidified with 2M hydrochloric acid to give isopropyl 3-hydroxythieno[2,3-c]pyridine-2-carboxylate, as a buff solid, which was collected by

filtration and dried, m.p. 176-7°, (Compound 14).

Example 15

1M Sodium hydroxide solution (51.6 ml) was added to a suspension of 2-mercaptonicotinic acid (8.0 g) in ethanol (100 ml) to give a clear, dark green solution. 1-Bromo-3,3-dimethyl-2-butanone (9.23 g) was then added and the mixture refluxed for 5 hours. The bulk of the solvent was evaporated and the residue treated with water (100 ml). The resultant mixture was filtered and the solid washed with water and dried to give the intermediate, 2-(3,3-dimethyl-2-oxobutylthio)nicotinic acid, m.p. 160-2°. This intermediate (2.53 g) was heated with potassium acetate (2.94 g) and acetic anhydride (20 ml) at reflux for 1 hour. After cooling, the reaction mixture was poured onto ice and extracted with ether. The extracts were washed with dilute aqueous sodium hydroxide, dried and evaporated to give an oil, which slowly solidified. Recrystallisation from hexane gave 2-(2,2-dimethyl-1-oxopropyl)thieno[2,3-b]pyridin-3-yl acetate, m.p. 60°, (Compound 15).

Example 16

A mixture of Compound 15 (6.40 g) and 1M aqueous sodium hydroxide (23 ml) in ethanol (50 ml) was heated at reflux for 3 hours. The bulk of the solvent was evaporated and the residue treated with water (20 ml) and then acidified with 3M hydrochloric acid. The mixture was extracted with ether and the extract evaporated. The residue was purified by silica gel column chromatography to give 2-(2,2-dimethyl-1-oxopropyl)-3-hydroxythieno-[2,3-b]pyridine, as a yellow-brown oil, (Compound 16).

Example 17

p-Toluenesulfonyl chloride (14.13 g) was added to a stirred suspension of Compound 1 (10.0 g) and anhydrous potassium carbonate (40.0 g) in acetone (200 ml). The mixture was stirred at room temperature for 4 hours and filtered. The filtrate was evaporated to give a colourless oil which was purified by silica gel column chromatography to give isopropyl 3-(p-toluenesulfonyloxy)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 102-4°. This compound (2.0 g) was heated with anhydrous potassium carbonate (0.71 g) and 1-butanethiol (0.46 g) in 2-butanone at reflux for 13 hours. The reaction mixture was cooled and filtered and the filtrate evaporated to give a yellow-brown oil which was purified by silica gel column chromatography to give isopropyl 3-(butylthio)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 38-9°, (Compound 17).

Example 18

Benzyl mercaptan (2.7 g) was added dropwise to a stirred suspension of sodium hydride (0.55 g) in tetrahydrofuran (10 ml) at 0° and under a nitrogen atmosphere. After cooling the mixture to -30°, Compound 10 (7.4 g) in tetrahydrofuran (20 ml) was added portionwise over 5 minutes. The mixture was stirred at room temperature for 2 hours before warming to 50° for 10 minutes. After cooling, the mixture was poured into ice-water (100 ml) and extracted with ethyl acetate. The extracts were washed with dilute aqueous sodium hydroxide and brine and then dried. Evaporation gave a dark oil which slowly solidified. Trituration with hexane then gave isopropyl 3-(benzylthio)thieno[2,3-b]pyridine-2-carboxylate. To a solution of this (2.50 g) in carbon tetrachloride (25 ml) was added, portionwise over 5 minutes, N-chlorosuccinimide (1.1 g). The mixture was stirred at room temperature for 1 hour and then at reflux for 45 minutes. After cooling and

filtering, the filtrate was evaporated to give a yellow oil which solidified on standing. To a vigorously stirred solution of 0.3 g of this material in tetrahydrofuran (15 ml) was added 3-bromopropyne (0.8 ml) followed by a solution of sodium carbonate (0.5 g) in water (5 ml). The mixture was stirred at room temperature for 10 minutes, diluted with water (10 ml) and extracted with diisopropyl ether. The extracts were washed with a saturated solution of sodium metabisulfite (20 ml), dried and evaporated to give a yellow solid which was triturated with diisopropyl ether to give isopropyl 3-(2-propynylthio)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 123.5-5.5°. (Compound 18).

Example 19

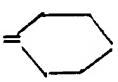
A mixture of methyl 2-mercaptonicotinate (2.94 g), bromoacetonitrile (2.05 g) and potassium carbonate (2.4 g) in acetonitrile (60 ml) was stirred at room temperature for 5 hours. The mixture was then poured into water (300 ml) and filtered to give the intermediate, methyl 2-(cyanomethylthio)nicotinate, as an off-white solid. After drying, the solid was added to potassium carbonate (2.26 g) and acetonitrile (50 ml) and the stirred mixture heated at reflux for 22 hours. The reaction mixture was poured into water (250 ml), filtered and the aqueous filtrate acidified with acetic acid. The precipitate was filtered and dried to give 3-hydroxythieno-[2,3-b]pyridine-2-carbonitrile, m.p. >265° (dec). (Compound 19)

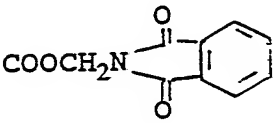
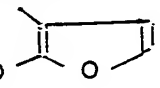
Example 20

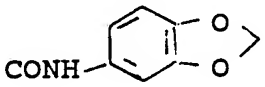
In a similar manner to one of the processes disclosed in the previous Examples, the compounds of formula I were obtained, in which the ring A is an unsubstituted pyrido ring, whose nitrogen is in the 7-position, except in those compounds, indicated with an asterisk, in which case it is in the 6-position, and Z is S. The Example method followed is given in the column headed "P". In the case of compounds made by the Example 19 method, the bromoacetyl intermediates were obtained by reacting an appropriate substrate with bromoacetyl bromide in ether or dichloromethane and in the presence of pyridine or triethylamine.

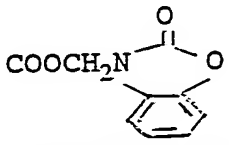
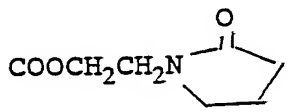
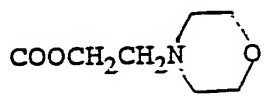
Cpd	R^1	X	R^2	P	m.p.(°)
20	$COO-CH_2Ph$	O	H	1	112-4
21	COOMe	O	CH_2CN	2	172
22	COOEt	O	$CH_2CH=CH_2$	2	81.5-3
23	COOEt	O	$CH_2C\equiv CH$	2	118-9
24	COOEt	O	CH_2CN	2	108.5-9.5
25	$COOPr^i$	O	$CH_2CH=CH_2$	2	72-3.5
26	$COOPr^i$	O	$CH_2C\equiv CH$	2	84.5-6
27	$COOPr^i$	O	CH_2Ph	2	oil
28	$COOPr^i$	O	$CH_2CH=CHPh$	2	oil
29	$COOPr^i$	O	$COCH=CH_2$	2	76
30	$COOPr^i$	O		2	oil
31	COOBu	O	CH_2CN	1+2	64
32	$COOBu^i$	O	CH_2CN	1+2	80-2
33	COOCH(Me)Pr	O	CH_2CN	1+2	70-2
34	$COO(CH_2)_5Me$	O	CH_2CN	1+2	57
35	COO-cyclohexyl	O	$CH_2C\equiv CH$	2	oil
36	COPh	O	CH_2CN	2	98-9

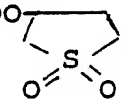
Cpd	R^1	X	R^2	P	m.p.(°)
37	CO(4-Cl-Ph)	O	CH_2CN	2	164
38	$CON(Pr^i)_2$	O	CH_2CN	2	88
39*	$COOPr^i$	O	CH_2CN	2	108-10
40	COOMe	O	$CH_2C\equiv CH$	3	147
41	$COOPr^i$	O	$CH_2CH_2C\equiv CH$	3	59-62
42	$COOPr^i$	O	$CH_2C\equiv CCH_2OH$	3	146
43	$COOPr^i$	O	CH(Me)CN	3	93-4
44	COOBu	O	$CH_2C\equiv CH$	1+3	59
45	$COO(CH_2)_5Me$	O	$CH_2C\equiv CH$	1+3	60-1
46	$COOCH_2Ph$	O	$CH_2C\equiv CH$	3	118-21
47	$CON(Pr^i)_2$	O	$CH_2C\equiv CH$	3	117
48	COPh	O	$CH_2C\equiv CH$	3	134
49	CO(4-Cl-Ph)	O	$CH_2C\equiv CH$	3	125
50*	$COOPr^i$	O	$CH_2C\equiv CH$	3	83-4
51	$COOPr^i$	O	CO(3-Me-Ph)	7	94-5
52	$COOPr^i$	O	$CO(2,4\text{-}Cl_2\text{-}Ph)$	7	130-1
53	$COOPr^i$	O	COPr	7	80-1
54	$COOPr^i$	O	$CO(4\text{-}NO_2\text{-}Ph)$	7	120-1.5
55	$COOPr^i$	O	COOMe	7	93-5
56	COO-cyclohexyl	O	CO(3-Me-Ph)	7	118-9
57	$COOPr^i$	O	$P(=S)(OEt)_2$	10	oil
58	COOEt	O	$CONH(CH_2)_5CN$	11	81-3.5
59	COO-cyclohexyl	O	$CONH(CH_2)_5CN$	11	90-2.5
60	$CON(Pr^i)_2$	O	COMe	15	oil
61	CO(4-Cl-Ph)	O	COMe	15	122-6
62	$CO(4\text{-}CF_3\text{-}Ph)$	O	COMe	15	138-40
63	CO(2-Cl-Ph)	O	COMe	15	93-5
64	COPh	O	COMe	15	133
65	COPh	O	H	16	122-4
66	$COOPr^i$	S	CH_2COOPr^i	17	54-5

Cpd	R^1	X	R^2	P	m.p.(°)
67	CONHPh	O	CO(4-NO_2-Ph)	7	188-9
68	CONHPh	O	COMe	7	166-7
69	COO-cyclohexyl	O	H	1	oil
70	$COOPr^i$	S	CH_2CH_2CN	18	110-2
71	$COOCH_2$-cyclohexyl	O	$CONH(CH_2)_5CN$	11	92-3
72	$COOCH(Me)-C_6H_{11}$	O	$CONH(CH_2)_5CN$	11	58-60
73	$COOC_7H_{13}$	O	$CONH(CH_2)_5CN$	11	75.5-6.5
74	2-furyl	O	H	1	210-3
75	$COOC_7H_{13}$	O	H	1	34-6
76	$COOCH_2$-cyclohexyl	O	H	1	122-5
77	$COOCH(Me)-C_6H_{11}$	O	H	1	oil
78	2-furyl	O	$CONH(CH_2)_5CN$	11	126-7.5
79	2-pyridyl	O	COMe	15	162-3.5
80	2-benzoxazolyl	O	COMe	15	199-200
81	2-benzoxazolyl	O	H	16	256-8.5
82	$COCH_2$-cyclohexyl	O	H	16	90-2
83	CO-cyclohexyl	O	H	16	69.5-72
84	COO-cyclohexyl	O	COMe	7	93-3.5
85	2-furoyl	O	COMe	15	129-30.5
86	2-furoyl	O	H	16	165-6
87	benzoyl	O	$CONH(CH_2)_5CN$	11	85-8
88	2-benzoxazolyl	O	$CONH(CH_2)_5CN$	11	138
89	2-pyridyl	O	H	16	183-4.5
90	5-Ph-oxazol-2-yl	O	COMe	15	179-80
91	COO(2,6-Me_2-Ph)	O	H	19	171-3
92	COS-cyclohexyl	O	H	19	103-4.5
93	$-PO(OPh)_2$	O	H	19	87-8
93		O	COMe	15	81-3

Cpd	R^1	X	R^2	P	m.p.(°)
94	-C(OCOMe)=CH-cyclohexyl	O	COMe	15	192-4
95	$COOPr^i$	O	COMe	7	oil
96	$COOPr^i$	NH	$(CH_2)_5CN$	5	66-7.5
97	$COOBu^i$	O	$CH_2C\equiv CH$	1+3	oil
98	COOCH(Me)Pr	O	$CH_2C\equiv CH$	1+3	oil
99	$COOCH_2Ph$	O	CH_2CN	2	105
100	$COBu^t$	O	$CH_2C\equiv CH$	3	oil
101	2-pyridyl	O	$CON(CH_2)_5CN$ | $CONH(CH_2)_5CN$	11	107-8.5
102	COO-cyclohexyl	O	$CONMe_2$	7	139-40.5
103	2-pyridyl	O	COOMe	7	168-9
104	2-furoyl	O	COOMe	7	139-40.5
105		O	H	19	208.4-10.5
106	$COOCH_2COEt$	O	H	19	159.1-60.4
107		O	H	19	146-50
108	$CON(Me)OCH_2(4\text{-}Cl\text{-}Ph)$	O	H	19	166.5-7.5
109	CON(OMe)-cyclohexyl	O	H	19	81-6
110	5-Ph-oxazol-2-yl	O	H	16	179-80
111	SO_2Ph	O	H	19	225-6
112	SPh	O	H	19	156-8
113	COOEt	O	H	1	68-70
114	COOCH(CN)Ph	O	H	19	196-8
115	COOH	O	CH_2Ph	4	152
116	2-(MeO)-Ph	O	H	19	144-5.5
117	$COOCH_2(4\text{-}NO_2Ph)$	O	H	19	193-6
118	2-(4-ClPh)thiazol-4-yl	O	H	19	103-5

Cpd	R^1	X	R^2	P	m.p.(°)
119	COOMe	O	Me	3	83-4
120	2-furyl	NH	H	13	144-5
121	4,6-$(MeO)_2$-pyrimidin-2-yl	O	H	19	176-8
122	NO_2	O	H	19	134-5
123	CO(2-ClPh)	O	H	16	156-8
124	CO(2-NO_2Ph)	O	H	16	216-9
125	CO(4-CF_3Ph)	O	H	16	148-50
126	CO(2,4-Cl_2Ph)	O	COMe	15	169-73
127	CO(2-NO_2Ph)	O	COMe	15	169-71
128	CO(4-CNPh)	O	COMe	15	140-2
129	CO(2,4-Cl_2Ph)	O	$CH_2C\equiv CH$	3	138-40
130	CO(2-pyridyl)	O	H	19	230-1
131	$CONPr^i_2$	O	H	16	100
132		O	H	9	253-4
133	$COBu^t$	O	CH_2CN	2	oil
134	CO(2,4-Cl_2Ph)	O	H	16	191-5
135	CO(4-ClPh)	O	H	16	172-4
136	CO(4-CNPh)	O	H	16	210-2
137	$COOPr^i$	O	$CH_2CH=CHCOOMe$	2	66
138	$COOPr^i$	O	CH_2COOEt	2	oil
139	$COOPr^i$	O	CH_2COOMe	2	78
140	$COOPr^i$	O	$CH_2C\equiv CMe$	3	82-3
141	$COOPr^i$	O	Bu^n	3	oil
142	$COOPr^i$	O	Pr^n	3	oil
143	$COOPr^i$	O	$CH_2C\equiv CPh$	3	oil
144	$COOPr^i$	O	$CH(Me)C\equiv CH$	3	oil
145	$COOPr^i$	O	$CH_2C\equiv CSiMe_3$	3	68-70
146	$COOPr^i$	O	$SiMe_2Bu^t$	6	107-8

Cpd	R^1	X	R^2	P	m.p.(°)
147	$COOPr^i$	O	SO_2(4-Me-Ph)	12	102-3.5
148	$COOPr^i$	S	CH_2Ph	18	oil
149	COO-cyclohexyl	NH	H	13	164.5-6.3
150	COO-cyclohexyl	O	$CH_2CH=CH_2$	2	oil
151	COO-cyclohexyl	O	CH_2CN	2	99-100
152	COO(2,6-Me_2Ph)	O	COMe	7	129-32
153		O	H	19	195.5
154	4,6-$(MeO)_2$-pyrimidin-2-yl	O	COMe	15	182-3
155		O	H	19	146-8
156	2-furyl	O	COOMe	7	173.2-5.1
157	2-thienyl	O	H	1	270(dec)
158	$COOCH_2$(4-MeO-Ph)	O	H	19	157-8
159	benzofuran-2-yl	O	H	19	286-90
160	COO-cyclohexyl	O	$CON(Me)(CH_2)_5CN$	7	oil
161	1,2,4-triazol-1-yl	O	H	19	214-9
162	CH=CHCOOMe	O	H	19	149-50
163	COO-cyclohexyl	O	$CSNMe_2$	7	oil
164	COO-cyclohexyl	O	COCOOEt	7	73-5
165	$COONEt_2$	O	H	19	73.5-6.5
166		O	H	1	147-50
167	$COOCH_2CH_2OCH_2CH_2OMe$	O	H	1	oil
168	$COOCH_2C\equiv CH$	O	H	19	113-6
169		O	H	1	116-9

Cpd	R^1	X	R^2	P	m.p.(°)
170	$COOCH_2CH_2SEt$	O	H	19	59-60
171	$COOCH_2CH=CH_2$	O	H	19	58-62
172		O	H	19	194-8
173	COMe	O	H	19	126.8-7.7
174	COO-cyclohexyl	O	cyclohexyl	3	oil
175	COOEt	O	Me	3	
176	COOMe	O	SO_2OPh	7	
177	1,2,4-oxadiazol-3-yl	O	H	19	
178	COO-cyclohexyl	O	$CONHNMe_2$	7	
179	COO-cyclohexyl	S	$4,6-(MeO)_2$-pyrimidin-2-yl	17	

Example 21

In a similar manner to that described in Example 14 there was obtained:

a) cyclohexyl 3-hydroxy-4-methylthiothieno-[3,2-c]quinoline-2-carboxylate. m.p. 152.5-3.5°. (Compound 210)

b) isopropyl 3-hydroxythieno[2,3-b]quinoline-2-carboxylate, m.p. 172.5-3.5°. (Compound 211)

c) cyclohexyl 3-hydroxythieno[2,3-b]quinoline-2-carboxylate, m.p. 146-7.5°. (Compound 212)

d) cyclohexyl 3-hydroxythieno[3,2-b]pyridine-2-carboxylate. (Compound 213)

d) cyclohexyl 3-hydroxythieno[3,2-c]pyridine-2-carboxylate N-oxide (Compound 214)

Example 22

A solution of compound 67 (2.8 g) in tetrahydrofuran (30 ml) containing a catalytic amount of 5% palladium on charcoal was stirred under an atmosphere of hydrogen until the theoretical amount of hydrogen had reacted. The mixture was then filtered through Kieselguhr and the filtrate evaporated to give a cream solid which was purified by silica gel column chromatography and recrystallisation from an ethyl acetate/hexane mixture to give isopropyl 3-(4-aminobenzoyloxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 161°. (Compound 220)

Example 23

In a similar manner to that described in Example 2,

a) compound 210 was converted to cyclohexyl 3-cyanomethoxy-4-methylthiothieno[3,2-c]quinoline-2-carboxylate, m.p. 155.5-6.5°. (Compound 230)

b) compound 211 was converted to isopropyl 3-cyanomethoxythieno[2,3-b]quinoline-2-carboxylate, m.p. 165.5-6°. (Compound 231)

c) compound 261 was converted to isopropyl 3-cyanomethoxy-4-methoxythieno[2,3-b]quinoline-2-carboxylate, m.p. 157-8.5°. (Compound 232)

Example 24

In a similar manner to that described in Example 11:

a) compound 210 was converted to cyclohexyl 3-(5-cyanopentylcarbamoyloxy)-4-methylthiothieno[3,2-c]quinoline-2-carboxylate, m.p 134-7°. (Compound 240)

b) compound 212 was converted to cyclohexyl 3-(5-cyanopentylcarbamoyloxy)thieno[2,3-b]quinoline-2-carboxylate, m.p. 106-13°. (Compound 241)

Example 25

In a similar manner to that described in Example 1,

a) ethyl 2-(isopropoxycarbonylmethylthio)-4-hydroxyquinoline-3-carboxylate, was converted to isopropyl 3,4-dihydroxythieno[2,3-b]quinoline-2-carboxylate, m.p. >430°. (Compound 250)

and there was also obtained:

b) cyclohexyl 3-hydroxy-6-methylthieno-[2,3-b]pyridine-2-carboxylate, m.p. 64-5.5° (Compound 251),

c) cyclohexyl 3-hydroxy-6-methoxythieno[2,3-b]pyridine-2-carboxylate, m.p. 97-101°, (Compound 252), and

d) cyclohexyl 3-hydroxy-5-nitrothieno[2,3-b]pyridine-2-carboxylate, (Compound 253).

The starting material for compound 250 was prepared as follows:

Phenyl isothiocyanate was reacted with diethyl sodiomalonate according to the method of Kay and Taylor (J.C.S. (C) (1968), 2656) and the resultant sodium salt (20 g), dissolved in dimethylformamide (60 ml), was treated with isopropyl bromoacetate (11.74 g). The mixture was stirred at room temperature for 27 hours and then left

to stand overnight. The mixture was poured into water and extracted with ether. The extracts were dried and evaporated to give an oily residue which was solidified by trituration with hexane. The solid was recrystallised from diisopropyl ether/hexane to give the intermediate, ethyl 2-(ethoxycarbonyl)-3-(isopropoxycarbonylmethylthio)-3-(phenylamino)propenoate, m.p. 63-4.5°. This product (3 g) in 1,2-dichlorobenzene (10 ml) was heated at reflux for 1 hour. The solvent was evaporated and the residue recrystallised from ethanol to give ethyl 2-(isopropoxycarbonylmethylthio)-4-hydroxyquinoline-3-carboxylate, m.p. 118.5-20°.

Example 26

Sodium hydride (0.47 g) was added to a stirred solution of ethyl 2-(isopropoxycarbonylmethylthio)-4-hydroxyquinoline-3-carboxylate (6.53 g) (starting material for compound 250) in dimethylformamide (100 ml) at room temperature. After stirring for 10 minutes, iodomethane (2.78 g) was added and the mixture stirred for a further 21.75 hours. The mixture was poured into sodium chloride solution and extracted with ether. The extracts were dried and evaporated to give an orange oil which was purified by silica gel column chromatography followed by preparative H.P.L.C. to give ethyl 2-(isopropoxycarbonylmethylthio)-4-methoxyquinoline-3-carboxylate, m.p. 48-53°.

Then in a similar manner to Example 1, this was reacted with sodium hydride in the presence of isopropanol to give isopropyl 3-hydroxy-4-isopropyloxythieno[2,3-b]quinoline-2-carboxylate, m.p. 115.5-7.5°. (Compound 260)

Also in a similar manner to Example 1, but using sodium methoxide in the presence of methanol, ethyl

2-(isopropoxycarbonylmethylthio)-4-methoxyquinoline-3-carboxylate was converted to isopropyl 3-hydroxy-4-methoxythieno[2,3-b]quinoline-2-carboxylate, m.p. 126-9.5°. (Compound 261)

This compound was then treated in a similar manner to that described in Example 3 to give isopropyl 4-methoxy-3-(propargyloxy)thieno-[2,3-b]quinoline-2-carboxylate, m.p. 119.5-20.5°. (Compound 262).

Example 27

In a similar manner to that described in Example 3,

a) compound 211 was converted to isopropyl 3-propargyloxythieno[2,3-b]quinoline-2-carboxylate, m.p. 142-3°. (Compound 270).

b) compound 210 was converted to cyclohexyl 4-methylthio-3-(propargyloxy)thieno[3,2-c]quinoline-2-carboxylate, m.p. 121-2.5°. (Compound 271)

Example 28

A solution of copper sulfate pentahydrate (0.58 g) in water (15 ml) was added to a warm solution of compound 69 (1 g) in ethanol (2.5 ml). The precipitate was filtered and dried to give the copper (II) salt of cyclohexyl 3-hydroxythieno[2,3-b]pyridine-2-carboxylate, as a light brown solid. (Compound 280).

Example 29

N-Iodosuccinimide (0.8 g) and silver nitrate (50 mg) were added to a stirred solution of Compound 26 (0.82 g) in acetone (30 ml). The resultant mixture was stirred for 30 minutes and, after standing overnight, was poured into water to give a cream solid. The solid was collected by filtration, washed with water, dried and then recrystallised from ethyl acetate to give isopropyl

3-(3-iodo-2-propynyloxy)thieno[2,3-b]pyridine-2-carboxylate, m.p. 187° (dec), Compound 290.

Example 30

A mixture of Compound 83 (1.4 g), methoxyamine hydrochloride (1.8 ml; 25 wt% solution in water) and sodium acetate (0.75 g) in ethanol (20 ml) was refluxed for 48 hours. After evaporating the solvent, the residue was purified by silica gel column chromatography to give an E/Z isomeric mixture of cyclohexyl (3-hydroxythieno-[2,3-b]pyridin-2-yl) ketone O-methyloxime, as a yellow oil, Compound 300.

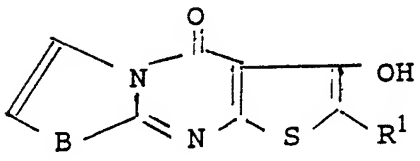
Example 31

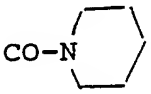
Compound 69 (1.0 g) was added to a solution of sodium hydroxide (0.145 g) in water (20 ml) and the mixture stirred for 45 minutes. After filtration, the filtrate was evaporated to give the sodium salt of cyclohexyl 3-hydroxythieno[2,3-b]pyridine-2-carboxylate as a pale yellow solid, m.p. 250° (dec), Compound 310.

Example 32

In a similar manner to that described in Example 14, ethyl 2-methylthio-4-oxo-4H-pyrido-[1,2-a]pyrimidine-3-carboxylate was reacted with cyclohexyl mercaptoacetate to give cyclohexyl 3-hydroxy-4-oxo-4H-pyrido-[1,2-a]thieno[2,3-d]pyrimidine-2-carboxylate, m.p. 142-5°. (Compound 320)

In a similar manner the following compounds were obtained.



Cpd No	B	R^1	m.p.(°)
321	-CH=CH-	$COO(CH_2)_6Me$	124-5
322	-CH=CH-	$COOCH_2$-cyclohexyl	174-5
323	-C(Me)=CH-*	COO-cyclohexyl	205-6
324	-S-	COO-cyclohexyl	211-2.5
325	-CH=CH-		solid
326	-CH=CH-	$COO-Pr^i$	161-4
327	-CH=CH-	COO-Me	234-6

* = Me is attached to position 8 of the ring

In a similar manner there was also obtained:

a) isopropyl 3-hydroxy-4-oxo-thieno[2'3':4,5]-4H-pyrimido[2,1-b]benzothiazole-2-carboxylate, m.p. 208.5-10.5° (Compound 328)

b) isopropyl 5-hydroxy-4-methoxy-2-phenylthieno-[2,3-d]pyrimidine-6-carboxylate, m.p 199-200°. (Compound 329),

c) cyclohexyl 5-hydroxy-2-methylthiothieno-[2,3-d]pyrimidine-6-carboxylate, m.p. 147-8° (Compound 329a),

d) cyclohexyl 3-amino-4-oxo-4H-pyrido[1,2-a]thieno-[2,3-d]pyrimidine-2-carboxylate, m.p. 161°. (Compound 329b),

e) methyl 5-hydroxy-2-methylthiothieno[2,3-d]pyrimidine-6-carboxylate, m.p. 223-4° (Compound 329c), and

f) cyclohexyl 7-aminothieno[2,3-b]pyrazine-6-carboxylate, m.p. 74-6. (Compound 329d).

Preparation of starting materials for compound 327 and 328

a) Starting material for compound 327

A stirred mixture of 2-aminobenzothiazole (12.1 g) and 5-[bis(methylthio)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (20 g) in N,N-dimethylformamide (1000 ml) was heated at reflux for 6.5 hours. After cooling, the intermediate 2-methylthio-4-oxo-4H-pyrimido-[2,1-b]benzothiazole-3-carboxylic acid was collected by filtration, washed with ethanol and dried. This acid (13.35 g) was refluxed with thionyl chloride (70 ml) for 7 hours. The excess thionyl chloride was then evaporated and the residue treated with ethanol (100 ml) and refluxed for 7 hours. After cooling the solvent was evaporated and the residue recrystallised from ethyl acetate to give the ethyl 2-methylthio-4-oxo-4H-pyrimido[2,1-b]benzothiazole-3-carboxylate, m.p. 193-4.5°.

b) Starting material for compound 328

Sodium hydride (84 mg) was added to a stirred solution of methyl 3,4-dihydro-6-methylthio-4-oxo-2-phenylpyrimidine-5-carboxylate (1.0 g) in dry dimethylformamide (20 ml). After stirring at room temperature for 15 minutes, dimethyl sulfate (0.46 g) was added and the mixture stirred for a further 18 hours. The mixture was poured into water and filtered to give a white solid. The solid was dissolved in ethyl acetate and filtered through kieselguhr. The filtrate was evaporated and the residue recrystallised from hexane to give the intermediate, methyl 4-methoxy-6-methylthio-2-phenylpyrimidine-5-carboxylate, m.p. 109-10.5°. The intermediate (0.58 g) was added to a mixture of glacial acetic acid (2 ml) and 30% hydrogen peroxide (2 ml) and stirred at 60° for 6.5

hours. The mixture was cooled and filtered to give a white solid. Recrystallisation of the solid from ethyl acetate-cyclohexane gave methyl 4-methoxy-6-methylsulfonyl-2-phenylpyrimidine-5-carboxylate, m.p 165-6°.

Example 33

Hydrogen peroxide (10 ml; 100 volumes) was added to a solution of Compound 329a (7.5 g) in acetic acid (100 ml) at 60°. The resulting solution was stirred overnight at room temperature and then poured into water to give a solid. The solid was collected by filtration, washed with water, dried and recrystallised from ethyl acetate/di-isopropyl ether to give cyclohexyl 5-hydroxy-2-methyl-sulfonylthieno[2,3-d]pyrimidine-6-carboxylate, m.p. 94-6°. (Compound 330)

Example 34

In a similar manner to that described in Example 3,

a) compound 329 (2.0 g) was converted to isopropyl 4-methoxy-2-phenyl-5-(propargyloxy)thieno-[2,3-d]pyrimidine-6-carboxylate, m.p. 157-8°. (Compound 340).

b) compound 382 (see in Example 38) was converted to 3-methoxy-2-(2-methoxypropyl)thieno[2,3-b]pyridine 1,1-dioxide, m.p. 149-52°. (Compound 341)

c) there was obtained 3-methoxy-2-methylthieno-[2,3-b]pyridine 1,1-dioxide. (Compound 342)

Example 35

In a similar manner to that described in Example 2, bromoacetonitrile was reacted with compound 326 to give isopropyl 3-cyanomethoxy-4-oxo-4H-pyrido[1,2-a]thieno-[2,3-d]pyrimidine-2-carboxylate, m.p. 190-1°. (Compound 350).

In a similar manner there was also obtained:

a) cyclohexyl 3-cyanomethoxy-4-oxo-4H-pyrido-[1,2-a]thieno-[2,3-d]pyrimidine-2-carboxylate, m.p. 225-7°. (Compound 351).

b) isopropyl 3-(5-cyanohexyloxy)-4-oxothieno[2′,3′:4,5]-4H-pyrimido[2,1-b]benzothiazole-2-carboxylate, m.p. 160.5-2° (Compound 352).

c) isopropyl 3-cyanomethoxy furo[2,3-b]pyridine-2-carboxylate, as an oil, (Compound 353).

d) isopropyl 5-cyanomethoxy-4-methoxy-2-phenylthieno-[2,3-d]pyrimidine-6-carboxylate, m.p. 199-200°. (Compound 354).

Example 36

In a similar manner to that described in Example 7,

a) compound 326 was reacted with 3-methylbenzoyl chloride to give isopropyl 3-(3-methylbenzoyloxy)-4-oxo-4H-pyrido-[1,2-a]thieno[2,3-d]pyrimidine-2-carboxylate, m.p. 208.5-10°. (Compound 360).

b) there was obtained isopropyl 3-(3-methylbenzoyloxy)-4-oxothieno-[2′3′:4,5]4H-pyrimido[2,1-b]benzo-thiazole-2-carboxylate, m.p. 204-6° (Compound 361),

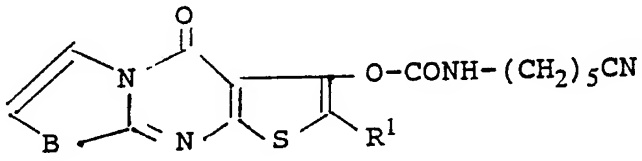
c) compound 251 was converted to cyclohexyl 3-acetoxy-6-methylthieno[2,3-b]pyridine-2-carboxylate, m.p. 81.5-3.5°. (Compound 362), and

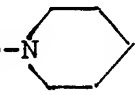
d) there was also obtained cyclohexyl 3-methoxycarbonyl-oxyfuro[2,3-b]pyridine-2-carboxylate, m.p. 94-7° (Compound 363).

Example 37

In a similar manner to that described in Example 5, isopropyl 3-hydroxy-4-oxo-4H-pyrido[1,2-a]thieno-[2,3-d]pyrimidine-2-carboxylate was reacted with butyl isocyanate to give isopropyl 3-(butylcarbamoyloxy)-4-oxo-4H-pyrido[1,2-a]thieno[2,3-d]pyrimidine-2-carboxylate, m.p. 180-2°. (Compound 370).

In a similar manner, starting from the appropriate compound from Example 32, the following compounds were obtained.



Cpd	B	R^1	m.p.(°)
371	-CH=CH-	COOEt	171-91
372	-CH=CH-	$COOPr^i$	171-5
373	-CH=CH-	COO-cyclohexyl	158-62
374	-CH=CH-	$COO(CH_2)_6Me$	148-9.5
375	-CH=CH-	$COOCH_2$-cyclohexyl	162-3
376	-CH=CH-		223-5
377	-C(Me)=CH-*	COO-cyclohexyl	166-8
378	-S-	COO-cyclohexyl	150-90(dec)
379	-CH=CH-	$COOCH_2Ph$	186-7

* = Me is attached to position 8 of the ring

In a similar manner there was also obtained: isopropyl 3-(5-cyanohexylcarbamoyloxy)-4-oxo-thieno[2',3':4,5]-4H-pyrimido[2,1-b]benzothiazole-2-carboxylate, m.p. 208.5-10.5° (Compound 379a).

Example 38

A mixture of methyl 2-mercaptonicotinate (3.38 g), cyclohexylmethyl bromide (2.8 ml) and potassium carbonate (2.76 g) in N,N-dimethylformamide (30 ml) was stirred for 4 hours. The mixture was poured into water (150 ml) and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a residue which was purified by silica gel column chromatography to give the intermediate, methyl 2-cyclohexymethylthionicotinate, as an oil. This intermediate (2.81 g) was stirred with 3-chloroperbenzoic acid (3.0 g, 50-60% pure) in dichloromethane (140 ml) overnight. The mixture was diluted with ethyl acetate (300 ml) and washed sequentially with water, aqueous sodium bicarbonate, aqueous ferrous sulfate, water and brine. After drying and evaporating, the residue was purified by silica gel column chromatography to give the intermediate, methyl 2-cyclohexylmethylsulfonylnicotinate, as an oil. This intermediate (2.35 g) in N,N-dimethylformamide (30 ml) was added dropwise, to a stirred suspension of sodium hydride (0.32 g) in N,N-dimethylformamide (10 ml). The mixture was stirred at room temperature overnight, then at 100° for 3 hours and finally at 140° overnight. After cooling, the mixture was treated with 0.8% aqueous sodium hydroxide (250 ml) and the resultant solution washed with dichloromethane. The aqueous phase was acidified with acetic acid and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was purified by silica gel column chromatography and recrystallisation from diisopropyl ether to give 2-cyclohexylthieno[2,3-b]pyridin-3(2H)-one 1,1-dioxide, m.p. 109-12°. (Compound 380).

In a similar manner there was obtained

a) 2-methylthieno[2,3-b]pyridin-3(2H)-one 1,1-dioxide, m.p. 108-10°, (Compound 381),

b) 2-(2-methoxypropyl)thieno[2,3-b]pyridin-3(2H)-one 1,1-dioxide, m.p. 128-31°, (Compound 382), and

c) 3-hydroxy-2-methylthieno[2,3-b]pyridine 1-oxide, (Compound 383).

Example 39

Compound 13 (2.75 g) and acetic anhydride (30 ml) were heated together at reflux for 3.5 hours. After cooling, the mixture was evaporated and the residue recrystallised from propane-2-ol to give isopropyl 3-(diacetylamino)-thieno[2,3-b]pyridine-2-carboxylate, m.p. 146-8°. (Compound 390).

Example 40

Hydrogen chloride gas was bubbled through a stirred solution of compound 19 (0.85 g) in methanol (30 ml), cooled in an ice-water bath, for 1 hour. The reaction vessel was sealed and allowed to stand at room temperature for 4 days. The mixture was then poured into aqueous sodium bicarbonate and extracted with ethyl acetate. The extract was dried and evaporated to give methyl 3-hydroxy-thieno[2,3-b]pyridine-2-carboximidate, m.p. 170° (dec). (Compound 400).

Example 41

A mixture of compound 69 (1.5 g) and N,N-dicyclohexyl-carbodiimide (1.12 g) was heated, in an oil bath at 168-178°, for 37 minutes. After cooling, the mixture was subjected to silica gel column chromatography to give the crude product which was purified further by dissolving in ether and washing with 10% aqueous sodium carbonate and water. The ether solution was dried and evaporated and the

residue dissolved in n-hexane and decanted from a small amount of insoluble gum. The n-hexane was evaporated to give cyclohexyl 3-[(cyclohexylamino)(cyclohexylimino)-methoxy]thieno[2,3-b]pyridine-2-carboxylate as a yellow sintered glass (83% purity by H.P.L.C). (Compound 410)

Example 42

Acetyl chloride (0.28 g) was added dropwise to a stirred solution of compound 149 (0.5 g) in tetrahydrofuran (20 ml) cooled in an ice-water bath. The mixture was stirred for 5 hours at room temperature and then triethylamine (0.2 g) was added dropwise. The mixture was poured into water and extracted with ether. The extracts were washed with water and aqueous sodium bicarbonate, dried and evaporated. The residue was recrystallised from diisopropyl ether to give cyclohexyl 3-acetamidothieno-[2,3-b]pyridine-2-carboxylate, m.p. 134-5°. (Compound 420)

In a similar manner there was also obtained cyclohexyl 3-(methoxycarbonylamino)thieno[2,3-b]pyridine-2-carboxylate, m.p. 93.5-5.5°. (Compound 421)

Example 43

Trifluoroacetic anhydride (0.3 ml) was added dropwise to a stirred solution of compound 149 (0.5 g) and triethylamine (0.26 ml) in dichloromethane (20 ml), cooled to -78°. The mixture was stirred at -78° for 1 hour and then allowed to warm up to room temperature overnight. The mixture was washed with 10% hydrochloric acid, dried and evaporated. Purification by silica gel column chromatography gave cyclohexyl 3-(trifluoromethylsulfonamido)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 300° (dec) (Compound 430), and cyclohexyl 3-[bis(trifluoromethylsulfonyl)-amino]thieno[2,3-b]pyridine-2-carboxylate, m.p. 149.5-50.5° (Compound 431).

In a similar manner, there was also obtained cyclohexyl 3-(methylsulfonamido)thieno[2,3-b]pyridine-2-carboxylate, m.p. 145-7°, (Compound 432).

Example 44

A mixture of compound 173 (0.8 g) and N,N-dimethyl-hydrazine (0.3 ml) in ethanol (50 ml) was refluxed for 4 hours. Evaporation of the solvent gave the dimethyl-hydrazone of 2-acetyl-3-hydroxythieno-[2,3-b]pyridine, m.p. 132.7-6.5°. (Compound 440).

Example 45

Diisobutylaluminium hydride (80 ml 1M solution in hexane) was added dropwise to a stirred solution of compound 119 (8.9 g) in tetrahydrofuran (250 ml) under a nitrogen atmosphere and cooled in order to keep the reaction mixture temperature below 15°. The mixture was then stirred at room temperature for 2 hours before an additional 40 ml diisobutylaluminium hydride solution was added. After stirring overnight, the reaction mixture was cooled and treated with dilute hydrochloric acid. The mixture was extracted with ethyl acetate and the extract dried and evaporated to give a residue which was purified by silica gel column chromatography to give 2-hydroxy-methyl-3-methoxythieno[2,3-b]pyridine, m.p. 84.5-6°, (Compound 450, and
3-methoxy-2-methylthieno[2,3-b]pyridine, as an oil, (Compound 451.

Example 46

A mixture of compound 4 (2.1 g) in diphenyl ether (10 ml) containing a catalytic amount of copper powder, was stirred and heated at 185° for 15 minutes. After cooling to room temperature, the mixture was purified by silica

gel column chromatography to give 3-methoxythieno-[2,3-b]pyridine, as a pale brown oil, (Compound 460)

Example 47

A mixture of compound 460 (0.4 g) and N-chlorosuccinimide (0.35 g) in carbon tetrachloride (50 ml) was refluxed for 3 hours. After cooling, the mixture was filtered and the filtrate evaporated to give an oily residue which was purified by silica gel column chromatography to give 2-chloro-3-methoxythieno[2,3-b]pyridine, m.p. 34-5°. (Compound 470).

Example 48

n-Butyllithium (5 ml 2.5 M solution in hexane) was added to a solution of compound 460 (0.83 g) in tetrahydrofuran (50 ml) cooled to -70°. After 10 minutes at this temperature, diethyl oxalate (2.1 ml) was added rapidly. The mixture was stirred for 1 hour, as it warmed to room temperature and was then poured into water (500 ml) and acidified with acetic acid. The mixture was extracted with ether and the extract was washed with water, dried and evaporated. The residue was purified by silica gel column chromatography and recrystallised from petroleum ether to give ethyl (3-methoxythieno[2,3-b]pyridin-2-yl)oxo-acetate, m.p. 93-6°. (Compound 480).

In a similar manner there was obtained:
3-methoxy-2-(4-butynoyl)thieno[2,3-b]pyridine. (Compound 481), and
3-methoxy-2-(2-propenoyl)thieno[2,3-b]pyridine. (Compound 482).

Example 49

n-Butyllithium (1.5 ml 2.5 M solution in hexane) was added to a solution of compound 460 (0.52 g) in tetrahydrofuran (50 ml) cooled to -70°. After 10 minutes, carbon disulfide (0.25 ml) was added. After a further 10 minutes, iodomethane (0.5 ml) was also added. The mixture was allowed to warm to room temperature and was then stirred for a further 1 hour before pouring into water (700 ml). The mixture was extracted with ether and the extract dried and evaporated. The residue was purified by silica gel column chromatography to give methyl 3-methoxythieno-[2,3-b]pyridine-2-carbodithiolate, as an oil, (Compound 490).

In a similar manner there was obtained:
ethyl 3-methoxythieno-[2,3-b]pyridine-2-sulfonate, (Compound 491).

Example 50

Sodium methoxide (1.7 g) was added to a stirred solution of cyanothioacetamide (3.0 g) in methanol (100 ml) at room temperature. After 15 minutes, 3,3-bis(methylthio)-2-cyanoacrylonitrile (5.1 g) was added and the mixture was stirred overnight. Cyclohexyl chloroacetate (5.3 g) was then added and the mixture stirred for a further 6 hours. The precipitate was collected by filtration, washed with methanol and recrystallised from acetonitrile to give the intermediate 2-amino-6-(cyclohexyloxycarbonylmethylthio)-4-methylthiopyridine-3,5-dicarbonitrile, m.p. 175-7°. Sodium hydride (0.16 g) was added to a stirred solution of this intermediate (1.5 g) in tetrahydrofuran (30 ml) at room temperature. After stirring overnight, the reaction mixture was poured into water to give a precipitate which was collected by filtration and purified by silica gel

column chromatography to give cyclohexyl 3,6-diamino-5-cyano-4-methylthiothieno[2,3-b]pyridine-2-carboxylate, m.p. 229-31°, (Compound 500).

Example 51

Trifluoroacetic anhydride (0.6 g) was added to a suspension of compound 13a (1.0 g) in toluene (25 ml). The resultant solution was stirred for 4 hours and was then left to stand overnight. Crystals appeared on standing which were collected by filtration, washed and dried to give cyclohexyl 5-chloro-4,6-dimethyl-3-trifluoro-acetamidothieno[2,3-b]pyridine-2-carboxylate, m.p. 144-6°, (Compound 510).

Example 52

Sodium hydride (0.9 g) was added portionwise to a stirred solution of ethyl 3-cyano-2-mercapto-6-methylpyridine-4-carboxylate (5.0 g) in tetrahydrofuran (30 ml). After 15 minutes, cyclohexyl bromoacetate (5.0 g) in tetrahydrofuran (20 ml) was added dropwise and the mixture stirred for a further 16 hours. Ethanol (3 ml) was added followed by water (100 ml). The mixture was extracted with ethyl acetate and the extract dried and evaporated. The residue was purified by silica gel column chromatography to give the intermediate, ethyl 3-cyano-2-(cyclohexyl-oxycarbonylmethylthio)-6-methylpyridine-4-carboxylate, m.p. 98-9°. Sodium hydride (0.4 g) was added to a solution of this intermediate (3.0 g) and the mixture stirred overnight at room temperature. The reaction mixture was poured into water (200 ml) to give a precipitate which was collected by filtration and recrystallised from diisopropyl ether to give 2-cyclohexyl 4-ethyl 3-amino-6-methylthieno-[2,3-b]pyridine-2,4-dicarboxylate, m.p.121-2°, (Compound 520).

Example 53

Pyridinium dichromate (0.91 g) was added portionwise to a stirred solution of compound 450 (0.5 g) in dichloromethane (20 ml) cooled in an ice bath. The resulting mixture was stirred overnight at room temperature. The reaction mixture was evaporated and the residue purified by silica gel column chromatography to give 3-methoxythieno[2,3-b]pyridine-2-carboxaldehyde, m.p. 115-7°, (Compound 530).

Example 54

Benzoyl chloride (0.26 ml) and triethylamine (0.32 ml) were added to a stirred solution of compound 450 (0.44 g) in dichloromethane (20 ml). After stirring overnight, the mixture was washed with water, dried and evaporated. The residue was purified by silica gel column chromatography to give 3-methoxythieno[2,3-b]pyridin-2-ylmethyl benzoate, m.p. 60.5-2.5°, (Compound 540)

Example 55

Sodium hydride (9.6 g) was added portionwise to a stirred solution of methyl 2-chloronicotinate (13.68 g) and cyclohexyl glycolate (12 g) in N,N-dimethylformamide (250 ml) cooled in an ice-water bath. The mixture was stirred for 18 hours at room temperature and was then poured into water, acidified and extracted with ether. The extract was dried, evaporated and the crude product purified by recrystallisation from diisopropyl ether followed by silica gel column chromatography to give cyclohexyl 3-hydroxyfuro[2,3-b]pyridine-2-carboxylate, m.p. 122.6-4.4, (Compound 550).

Example 56

Compound 330 (1.6 g) was added to a solution of sodium methoxide (0.5 g) in methanol (20 ml) and the mixture heated at reflux for 4 hours. After cooling, the mixture was poured into water and acidified. The mixture was then extracted with ether and the extract dried and evaporated to give a residue which was recrystallised from diisopropyl ether to give cyclohexyl 5-hydroxy-2-methoxy-thieno[2,3-d]pyrimidine-6-carboxylate, m.p. 112-3°. (Compound 560)

In a similar manner compound 330 was converted to

a) cyclohexyl 5-hydroxy-2-phenoxythieno[2,3-d]-pyrimidine-6-carboxylate, m.p. 170-1°. (Compound 561) and

b) cyclohexyl 5-hydroxy-2-isopropylthiothieno[2,3-d-pyrimidine-6-carboxylate, m.p. 91-2°. (Compound 562)

Example 57

Sodium metal (0.25 g) was dissolved in diethylamine (25 ml) over 2 days. Compound 330 (2.0 g) was then added and the mixture refluxed for 6 hours. After cooling the supernatant was poured into water and acidified with hydrochloric acid to give a precipitate which was collected by filtration, washed with water and dried. The solid was recrystallised from ethyl acetate to give cyclohexyl 2-diethylamino-5-hydroxythieno-[2,3-d]pyrimidine-6-carboxylate, m.p. 120-1°. (Compound 570)

Example 58

A mixture of compound 382 (0.5 g), phenylhydrazine (0.19 ml) and a catalytic amount of p-toluenesulfonic acid in toluene (70 ml) was heated at reflux for 3 hours. After cooling, the mixture was filtered and the filtrate

evaporated. The residue was triturated with ether and filtered to give a solid comprising the E and Z isomers of the phenylhydrazone derivative of 2-(2-methoxypropyl)-thieno-[2,3-b]pyridin-3(2H)-one 1,1-dioxide, m.p. 136-42°. (Compound 580)

In a similar manner there was obtained:
2-(2-methoxypropyl)thieno-[2,3-b]pyridin-3(2H)-one 1,1-dioxide O-ethyloxime, (Compound 581).

Example 59

Compound 4 (0.76 g) and thionyl chloride (15 ml) were refluxed together for 5 hours. The mixture was evaporated to give the intermediate 3-methoxythieno[2,3-b]pyridine-2-carbonyl chloride which was dissolved in dichloromethane (15 ml) and added dropwise to a stirred, ice-cooled solution of 4-chlorophenol (0.46 g) and triethylamine (0.56 ml) in dichloromethane (10 ml). The mixture was stirred at room temperature overnight and then washed with water and aqueous sodium bicarbonate. After drying, the mixture was evaporated and the residue purified by silica gel column chromatography to give 4-chlorophenyl 3-methoxythieno[2,3-b]pyridine-2-carboxylate, m.p. 135-6°. (Compound 590)

In a similar manner there was obtained:

a) N-cyclohexyl-3-methoxythieno[2,3-b]pyridine-2-carboxamide, (Compound 591), and

b) N-(dimethylamino)-3-methoxythieno[2,3-b]pyridine-2-carboxamide, (Compound 592).

Example 60

A mixture of 2-cyano-3-(2-thienyl)propenethioamide (8.0 g), 2,4-pentanedione (4.3 g) and piperidine (16 drops) in ethanol (80 ml) was stirred at reflux for 23 hours. The mixture was cooled and filtered to give a solid which was washed with ethanol and ether and then dried to give the intermediate 5-acetyl-3-cyano-6-methyl-4-(2-thienyl)-2(1H)-pyridinethione, m.p. c.240° (dec). Potassium t-butoxide (0.84 g) was added portionwise to a stirred solution of the intermediate (2.0 g) in N,N-dimethylformamide (15 ml), cooled in an ice-bath. Methyl bromoacetate (1.15 g) was then added and the mixture stirred for 10 minutes with cooling and 1.5 hours at room temperature. After standing overnight, the mixture was added to ice-water and filtered. The solid was washed with water and then dried. Trituration with ethyl acetate, followed by cooling in ice and filtration then gave methyl 5-acetyl-3-amino-6-methyl-4-(2-thienyl)thieno-[2,3-b]pyridine-2-carboxylate, m.p. 208-10°. (Compound 600)

In a similar manner there was obtained:
cyclohexyl 5-acetyl-3-amino-4,6-dimethylthieno-[2,3-b]pyridine-2-carboxylate, (Compound 601)

Example 61

Compound 470 was reacted with phenylacetylene in the presence of a palladium(0) catalyst to give 3-methoxy-2-(phenylethynyl)thieno[2,3-b]pyridine. (Compound 610)

Example 62

Compound 591 was reacted with phosphoryl chloride followed by cyclohexylamine to give N,N'-dicyclohexyl-3-methoxy-thieno[2,3-b]pyridine-2-carboxamide. (Compound 620)

Example 63

Compound 530 was reacted with ethylene glycol in the presence of an acid catalyst to give 2-(2-dioxolanyl)-3-methoxythieno[2,3-b]pyridine. (Compound 630)

Example 64

Methyl 3-hydroxythieno-[2,3-b]pyridine-2-carboxylate was converted to its sodium salt which was then reacted with carbon disulfide and iodomethane to give methyl 3-(methylthiothiocarbonyloxy)thieno[2,3-b]pyridine-2-carboxylate. (Compound 640)

Example 65

Methyl 3-hydroxythieno-[2,3-b]pyridine-2-carboxylate was converted to its sodium salt which was then reacted with bis(4-chlorophenyl)trithiocarbonate to give methyl 3-[(4-chlorophenyl)thiothiocarbonyloxy]thieno[2,3-b]-pyridine-2-carboxylate. (Compound 650)

Example 66

Methyl 3-hydroxythieno-[2,3-b]pyridine-2-carboxylate was reacted with hydrazine hydrate to give 3-hydroxy-[2,3-b]pyridine-2-carbohydrazide which was reacted with acetic anhydride followed by polyphosphoric acid to give 3-hydroxy-2-(5-methyl-1,3,4-oxadiazol-2-yl)thieno-[2,3-b]pyridine. (Compound 660)

Test Example

Compounds are assessed for activity against one or more of the following:

Plasmopara viticola: vine downy mildew (PV)

Erysiphe graminis: barley powdery mildew (EG)

Pyricularia oryzae: rice blast (PO)

Pellicularia sasakii: rice sheath blight (PS)

Botrytis cinerea: grey mould of tomato (BC)

Venturia inaequalis: apple scab (VI)

Leptosphaeria nodorum: glume blotch (LN)

Pseudocercosporella herpotrichoides: eyespot (PH)

Aqueous solutions or dispersions of the compounds at the desired concentration, including a wetting agent, were applied by spray or by drenching the stem base of the test plants, as appropriate. Plants or plant parts were then inoculated with appropriate test pathogens and kept under controlled environment conditions suitable for maintaining plant growth and development of the disease. After an appropriate time, the degree of infection of the affected part of the plant was visually estimated. Compounds were considered active if they gave greater than 50% control of the disease at a concentration of 500 ppm (w/v) or less. The following known compounds were also tested:

Compound A: methyl 3-hydroxythieno-[2,3-b]pyridine-2-carboxylate

Compound B: ethyl 3-hydroxy-4-oxo-4H-pyrido-[1,2-a]thieno[2,3-d]pyrimidine-2-carboxylate.

Activities were demonstrated as follows (+ = active).

Compound No	PV	EG	PO	PS	BC	VI	LN	PH
1						+		
2		+	+					
3	+							
4	+							
5a	+					+		+
5b		+						
6						+		+
7	+							
8	+		+					
9	+		+					
10		+						
11	+		+					
12				+				
13	+					+		
13a			+					
14	+	+	+			+		
15	+		+				+	
16	+							+
17						+		
18		+						
19	+		+					
20	+					+		
21							+	
22						+		
23						+		
24	+							
25	+			+				
26	+		+			+		
27			+					
28			+					
29	+				+	+		
30								+

Compound No	PV	EG	PO	PS	BC	VI	LN	PH
31	+	+				+		
32	+							
33	+							
34	+					+		
35	+							
36								+
37			+					
38								+
39						+		
40	+							
41	+							
42					+	+		
43				+				
44						+		
45	+							
46	+				+			
47	+	+						
48	+							
49		+				+		
50	+					+		
51						+		
52						+		
53						+		
54	+					+		
55	+		+			+		
56						+		
57	+					+		
58	+		+					+
59	+					+		
60		+						
61	+							
62	+					+		

Compound No	PV	EG	PO	PS	BC	VI	LN	PH
63			+			+	+	
64					+	+		+
65	+		+					
66				+				
67	+							
68	+							
69							+	
71	+	+	+				+	
72	+	+	+					
73	+	+	+					
74			+					
75		+						
76	+		+					
77							+	
78		+	+			+		
79		+		+				
80	+					+		
81			+					
82			+					
83			+					
84						+		
85	+							
86			+					
87			+					
88			+					
89	+					+	+	
90			+					
91	+		+					
92			+					
93			+					
95	+					+		
96	+					+		

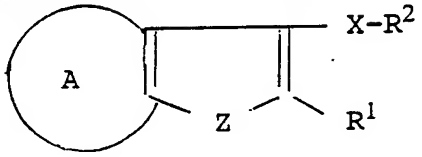
Compound No	PV	EG	PO	PS	BC	VI	LN	PH
97	+							+
98	+							
99						+		
100						+		
101		+				+		
102	+							
103	+							
104		+						
105						+		
106		+						
107		+						
108	+							
109	+							
110	+							
111					+			
112					+			
113			+					
114						+		
115			+				+	
116						+		
117						+		
118	+							
119							+	
126						+		
127						+		
128						+		
129			+			+	+	
130	+							
132	+			+				
133			+					
135						+		
136						+	+	

Compound No	PV	EG	PO	PS	BC	VI	LN	PH
141							+	
142							+	
144						+		
147	+		+			+		
150						+		
152						+		
155							+	
158							+	
167			+					
168	+							
211	+							
230	+					+		
231						+		
232						+		
240		+	+					
241	+							
250			+					
260	+							
261						+		
262	+					+		
270						+	+	
271						+		
280			+					
290			+					
300		+	+					
310	+							
320			+					
321						+		
322			+					
323	+							
324	+	+	+				+	
326								+

Compound No	PV	EG	PO	PS	BC	VI	LN	PH
327					+		+	
329			+					
329a				+				
330		+		+				
340		+						
350						+		
351						+	+	
352						+	+	
353						+		
354						+		
360			+					
361	+							
362	+							
367						+		
370				+				
371	+		+			+		
372			+			+		
373	+		+			+		
374	+				+	+		
375	+					+		
376	+	+			+	+		
377	+		+			+		
378	+			+		+	+	
379						+		
379a		+		+			+	
390						+		
550	+	+				+		
562	+							
A						+		+
B	+			+				

CLAIMS

1. The use for combating phytopathogenic fungi, of a compound of formula I



(I)

where

ring A is an optionally substituted six membered ring containing one or two nitrogen atoms;

X is O, S or $-NR^3-$;

R^1 is Q, cyano, halogen or nitro;

Q is hydrogen, acyl, $-C(=W)R^5$, $-SR^3$, $-C(=NR^3)NR^4R^5$, $-C(=NR^3)OR^4$, $-C(OR^5)R^3R^4$, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl;

R^2 is Q, or $-SiR^3R^4R^5$, or when X is O or NR^3, can also be $-NR^4R^5$, or when X is NR^3, can also be $-OR^4$;

W is NR^3, NOR^3 or NNR^4R^5;

Z is $S(O)_n$ or O;

R^3, R^4 and R^5, which may be the same or different, are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heterocyclyl or R^3 and R^4 or R^4 and R^5 together with the atom to which they are attached can form a ring;

and

n is 0, 1 or 2, together with salts of compounds which are acidic and also complexes with metal salts, with the proviso that when the compound is a thieno[2,3-d]pyrimidine, where X is O and R^2 is (halo)alkyl, it is not substituted in the 4-position by optionally substituted amino.

2. Compounds of formula I as defined in claim 1, with with the provisos, when Z is S:

(i) X is not NR^3, where R^3 is hydrogen;

(ii) when X is oxygen and R^2 is hydrogen, optionally substituted alkyl, cycloalkyl, $-COR^3$, $-COOR^3$, $-CONR^3R^4$ or $-COSR^3$, then R^1 is not optionally substituted alkyl (except cyanoalkyl), optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl or heteroaryl,

(iii) when ring A is pyrido, with the N-atom in the 5-position, the ring is not monosubstituted in the 4-position by aroyl or in the 4 or 6 position by methyl,

(iv) when ring A is pyrido, with the N-atom in the 6-position, R^1 is not hydrogen or methyl,

(v) when ring A is pyrido, with the N-atom in the 7-position, X is oxygen and R^2 is hydrogen, then R^1 is not a) COD or C(=NH)D, where D is optionally substituted alkoxy, optionally substituted cycloalkoxy or $-NR^3R^4$, nor b) $-C(=NR^3)NR^4R^5$, in which R^3 and R^4 together with the atom to which they are attached form a 5 or 6 membered ring, and

(vi) when ring A is pyrido, with the N-atom in the 7-position, the ring is not monosubstituted in the 4-position by amino or methyl.

(vii) when the compound is a thieno[2,3-d]pyrimidine, carrying a ring fused to the pyrimidine it is not substituted in the 4-position by oxo.

(viii) when the compound is a thieno[2,3-d]pyrimidine, and X is S, R^2 is not hydrogen.

(ix) when ring A is pyrido, with the N-atom in the 5-position, it is not a tetrahydropyrido ring,

and with the further proviso that when Z is O or S and ring A is pyrido, the pyrido ring does not carry an

imidazolinyl grouping.

3. The isopropyl, cyclohexyl and benzyl esters of 3-hydroxythieno[2,3-b]pyridine-2-carboxylic acid.

4. 3-Hydroxythieno[2,3-b]pyridine, substituted in the 2-position by phenylcarbamoyl, furyl, pyrid-2-yl, 5-phenyloxazol-2-yl or benzoxazol-2-yl.

5. A method of combating phytopathogenic fungi at a locus infested or liable to be infested therewith, which comprises applying to the locus a compound of formula I as defined in claim 1.